Immunology

THIRD EDITION

Peter Lydyard
Alex Whelan
Michael Fanger

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BIOS INSTANT NOTES

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Preface

Immunology as a science probably began with the observations by Metchnikoff in 1882 that starfish when pierced by a foreign object (a rose thorn) responded by coating it with cells (later identified as phagocytes). Immunology—the study of the way in which the body defends itself against invading organisms or internal invaders (tumors)—has developed rapidly over the last 50 years, and more recently with the advent of molecular techniques has contributed critical tools for research and diagnosis, and therapeutics for treatment of a wide range of human diseases.

Immunology has thus become an integral part of human and life science courses as well as medical studies. In this third edition, we have included some of the recent important aspects of immunology and have (1) updated all of the material presented, including adding more figures and tables; (2) emphasized the important role of pattern recognition in immune responses; (3) described critical aspects of antigen processing and presentation to T cells in more detail; (4) described the recent advances in our understanding of how immune responses are regulated, particularly through regulatory T cells and the neuroendocrine system; (5) described important microbial infections in some detail from entry of the microbe to mechanisms of immunity; (6) made more definitive the material on the role of age and gender on immune responses; (7) added a new chapter on immunotherapy for the treatment of a number different diseases.

Overall, we believe that this third edition of *Instant Notes in Immunology* will provide a firm basis for the understanding of contemporary human immunology and its relevance to the mechanisms and treatments of human diseases.

For ease of understanding, we have divided the subject matter in this book into seven main areas:

1. Cellular and molecular components of the immune system (Sections A–D).
2. Mechanisms involved in the development of immunity (Sections E–G), including antibody and cellular responses, and their regulation.
3. The immune system in action (Sections H and I), including immunity to infection and vaccination.
4. Diseases and deficiencies of the immune system (Sections J–L), including allergy, autoimmunity, and congenital and acquired immune deficiency.
5. The immune response to tumors and transplants (Sections M and N).
6. The influence of gender and aging on the immune response (Sections O and P).
7. A new chapter on immunotherapy including monoclonal antibodies, cytokines, and cellular therapy (Section Q).

We are grateful for the helpful discussions with Dr Michael Cole, Professor Peter Delves, Dr Derek Doherty, Professor Paul Guyre, Dr Aideen Long, Professor Randy Noelle, and Dr Mark Smith.

We would also like to thank our wives, Meriel, Annette, and Sharon for longstanding support and understanding during preparation of the third edition.

PML, AW, and MWF

A1 The need

Key Note

The ubiquitous enemy	Infectious microbes and larger organisms such as worms are present in our environment. They range from being helpful (e.g., *E. coli*) to being major pathogens which can be fatal (e.g., HIV).
Related topic	(H1) The microbial cosmos

The ubiquitous enemy

Microbes are able to survive on animal and plant products by releasing digestive enzymes directly and absorbing the nutrients, and/or by growth on living tissues (extracellular), in which case they are simply bathed in nutrients. Other microbes infect (invade and live within) animal/human cells (intracellular), where they not only survive, but also replicate utilizing host-cell energy sources. Both extracellular and intracellular microbes can grow, reproduce, and infect other individuals. There are many different species of microbes and larger organisms (such as worms) that invade humans, some of which are relatively harmless and some even helpful (e.g., *E. coli* in the intestines). Many others cause disease (human pathogens). There is a constant battle between invading microbes and the immune system (Section H2). Although most pathogenic microbes do not cause mortality, they do produce global morbidity. Table 1 shows the range of organisms that can infect humans.

Table 1. Range of infectious organisms

Worms (helminths)	e.g., tapeworms, filaria
Protozoans	e.g., trypanosomes, leishmania, malaria
Fungi	e.g., *Candida*, *Aspergillus*
Bacteria	e.g., *Bacteroides*, *Staphylococcus*, *Streptococcus*, mycobacteria
Viruses	e.g., polio, pox viruses, influenza, hepatitis B, human immunodeficiency virus (HIV)
Prions	e.g., Creutzfeldt–Jakob disease (CJD)

A2 External defenses

Key Notes

Physical barriers to entry of microbes	Microbes gain entrance into the body actively (penetration of the skin), or passively (ingestion of food and inhalation). They have to pass across physical barriers such as the skin or epithelial cells which line the mucosal surfaces of the respiratory, gastrointestinal, and genitourinary tracts.
Secretions	Secretions from epithelial surfaces at external sites of the body are important for protection against entry of microbes. Sweat, tears, saliva, and gastric juices all contain antimicrobial substances such as enzymes, peptides (e.g., defensins), fatty acids, and secreted antibodies.
Microbial products and competition	Nonpathogenic bacteria (commensals) colonize epithelial surfaces, and by releasing substances toxic to other microbes, for example colicins, competing for essential nutrients required by pathogens, and occupying the microenvironment, they prevent invasion by pathogenic bacteria.
Related topics	(C3) Mucosa-associated lymphoid tissues (H1) The microbial cosmos

Physical barriers to entry of microbes

Before a microbe or parasite can invade the host and cause infection, it must first attach to and penetrate the surface epithelial layers of the body. Organisms gain entrance into the body by active or passive means. For example, they might burrow through the skin, be ingested in food, be inhaled into the respiratory tract, enter via the genitourinary tract, or penetrate through an open wound. In practice, most microbes take advantage of the fact that we have to breathe and eat, and therefore enter the body through the respiratory and gastrointestinal tracts. Whatever their point of entry, they have to pass across physical barriers such as the dead layers of the skin or living epithelial cell layers which line the cavities in contact with the exterior—the respiratory, genitourinary, and gastrointestinal tracts. These are the main routes of entry of microbes into the body.

Many of the cells at the interface with the outside world are mucosal epithelial cells, which secrete mucus. In addition to providing a physical barrier, these cells have other properties useful in minimizing infection. For example, epithelial cells of the nasal passages and bronchi of the respiratory system have **cilia** (small hair-like structures) that beat in an upward direction to help remove microorganisms that enter during breathing. This is the **mucociliary escalator** (Figure 1).

Secretions

A variety of secretions at epithelial surfaces are important in defense (Table 1), as they help to create a hostile environment for microbial habitation. Some substances are known to directly kill microbes, for example lysozyme digests proteoglycans in bacterial cell walls;

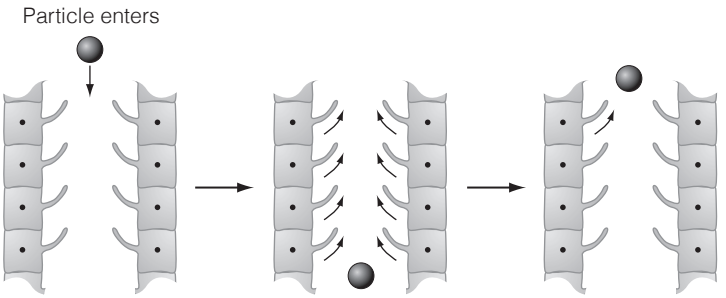

Figure 1. The mucociliary escalator. When a particle is inhaled, it comes into contact with cilia of the bronchial or nasal epithelia, which beat in an upwards direction to a position where the particle can be coughed up or sneezed out.

Table 1. Secretions at epithelial surfaces

Site	Source	Specific substances secreted
Eyes	Lacrimal glands (tears)	Lysozyme, IgA and IgG, antimicrobial peptides*
Ears	Sebaceous glands	Oily waxy secretion, fatty acids
Mouth	Salivary glands (saliva)	Digestive enzymes, lysozyme, IgA, IgG, lactoferrin
Skin	Sweat glands (sweat)	Lysozyme, high NaCl, short-chain fatty acids
	Sebaceous glands	Oily secretion and fatty acids (sebum)
Stomach	Gastric juices	Digestive enzymes (pepsin, rennin), acid (low pH, 1–2)

* Antimicrobial peptides are found in all of these secretions.

others, for example transferrin, compete for nutrients (i.e., Fe), and others interfere with ion transport (e.g., NaCl). Mucus (containing mucin) secreted by the mucosal epithelial cells coats cell surfaces and makes it difficult for microbes to contact and bind to these cells—a prerequisite for entry into the body.

The washing action of tears, saliva, and urine also helps to prevent attachment of microbes to the epithelial surfaces. In addition, IgA **antibodies** in tears and saliva prevent the attachment of microbes. These antibodies are also secreted across epithelial cells into the respiratory, gastrointestinal, and genitourinary tracts (Sections C3 and O1).

A large number of different antimicrobial peptides, produced by epithelial cells in the respiratory, gastrointestinal, and genitourinary tracts, are found in body secretions (Table 1). These peptides, which are also produced by phagocytic cells, have potent antibacterial properties and include cecropins, magainins, and defensins (Section B2).

Microbial products and competition

Normal commensals (**nonpathogenic bacteria**) are also important in protection from infection. These nonpathogenic microorganisms are found on the skin, in the mouth, and in the reproductive and gastrointestinal tracts. The gastrointestinal tract contains many billions of bacteria that have a symbiotic relationship with the host. These bacteria help to prevent pathogens from colonizing the site by preventing attachment, competing for essential nutrients, and releasing antibacterial substances such as **colicins** (antibacterial proteins) and short-chain fatty acids. Gut flora also perform such house-keeping

duties as further degrading waste matter and helping gut motility. Normal microbial flora occupying the site of entry (e.g., throat and nasal passages) of other microbes probably function in a similar manner. Some commensal bacteria such as lactobacilli, which inhabit the vagina, cause their environment to become acidic (pH 4.0–4.5), discouraging the growth of many microbes (Section O2).

A3 Immune defense

Key Notes

The immune system

The immune system protects us from attack by microbes and worms. It uses specialized organs designed to filter out and respond to microbes entering the body's tissues and a mobile force of molecules and cells in the bloodstream to respond rapidly to attack. The system can fail, giving rise to immunodeficiency, or "over-react" against foreign microbes, giving rise to tissue damage (immunopathology). It has complex and sophisticated mechanisms to regulate it.

Innate versus adaptive immunity

The innate immune system is the first line of defense against infection. It works rapidly, gives rise to the acute inflammatory response, and has some specificity for microbes, but has no memory. In contrast, the adaptive immune system takes longer to develop, is very highly specific, and responds more quickly to a microbe that it has encountered previously (i.e., shows memory).

Interaction between innate and adaptive immunity

The innate and adaptive immune systems work together through direct cell contact and through interactions involving chemical mediators, cytokines, chemokines, and antibodies. Moreover, many of the cells and molecules of the innate immune system are also used by the adaptive immune system.

Adaptive immunity and clonal selection

All immunocompetent individuals have many distinct lymphocytes, each of which is specific for a different foreign substance (antigen). When an antigen is introduced into an individual, lymphocytes with receptors for this antigen seek out and bind it and are triggered to proliferate and differentiate, giving rise to clones of cells specific for the antigen. These cells or their products specifically react with the antigen to neutralize or eliminate it. The much larger number of antigen-specific cells late in the immune response is responsible for the "memory" involved in adaptive immunity.

T and B cells and cell cooperation

There are two major types of lymphocytes: B cells and T cells. T cells mature under the influence of the thymus and, on stimulation by antigen, give rise to cellular immunity. B cells mature mainly under the influence of bone marrow and give rise to humoral immunity, immunity that involves production of soluble molecules—**antibodies** (**immunoglobulins**). Interactions between T and B cells, as well as between T cells and antigen-presenting cells, are critical to the development of specific immunity.

Related topics		
(C) The adaptive immune system	(F) The T-cell response – cell-mediated immunity	
(D) Antibodies	(G) Regulation of the immune response	
(E3) The cellular basis of the antibody response	(H) Immunity to infection	

The immune system

The immune system is composed of many cell types, the majority of which are organized into separate lymphoid tissues and organs (Section C2). Because attack from microbes can come at many different sites of the body, the immune system has a mobile force of cells in the bloodstream that are ready to attack the invading microbe wherever it enters the body. Although many of the cells of the immune system are separate from each other, they maintain communication through cell contact and molecules secreted by them (such as cytokines and chemokines). Like the other body systems, the immune system is only apparent when it goes wrong. This can lead to severe, sometimes overwhelming, infections and even death. One form of dysfunction is **immunodeficiency**, which can, for example, result from infection with the human immunodeficiency virus (HIV) causing acquired immune deficiency syndrome (AIDS). On the other hand, the immune system can be "hypersensitive" to a microbe (or even to "an inert" substance such as pollen) and this itself can cause severe tissue damage sometimes leading to death. Thus, the immune system must strike a balance between producing a life-saving response and a response that causes severe tissue damage. This regulation (Section G) is maintained by cells and molecules of the immune system (e.g., regulatory T cells-Tregs, and cytokines) and from without by nonimmune cells and tissues and their products (e.g., the neuroendocrine system).

Innate versus adaptive immunity

Having penetrated the external defenses, microbes come into contact with cells and products of the immune system and the battle commences. A number of cell types and defense molecules are usually present at the site of invasion, or migrate (**home**) to the site. This "first line of defense" is the "**innate immune system**." It is present at birth and changes little throughout the life of the individual. The cells and molecules of this innate system are mainly responsible for the first stages of expulsion of the microbe and may give rise to inflammation (Section B4). Some of the most important cells in the innate immune system are phagocytes, because they are able to ingest and kill microbes.

The second line of defense is the "**adaptive immune system**," which is brought into action even as the innate immune system is dealing with the invading microbe, and especially if it is unable to remove it. The key difference between the two systems is that the adaptive system shows far more specificity and remembers that a particular microbe has previously invaded the body. This leads to a more rapid expulsion of the microbe on its second or third time of entry. The cells, molecules, and characteristics of innate and adaptive immune systems are shown in Table 1.

Interaction between innate and adaptive immunity

Although innate and adaptive immunity are often considered separately for convenience and to facilitate their understanding, it is important to recognize that they work together. For example, macrophages are phagocytic but produce important **cytokines** (Section B2)

Table 1. The innate and adaptive immune systems

Characteristics	Cells	Molecules
Innate immunity		
Responds rapidly	Phagocytes (PMNs and macrophages)	Antimicrobial peptides
		Complement
Has some specificity	Natural killer cells	Cytokines
But no memory	Mast cells	Chemokines
	Dendritic cells	Acute phase proteins
Adaptive immunity		
Slow to start	T and B cells	Antibodies
Highly specific		Cytokines
Memory		Chemokines

that help to induce the adaptive immune response. Cytotoxic T cells kill virus-infected body cells. These have to be cleared from the body by phagocytic cells. Complement components of the innate immune system can be activated directly by microbes, but can also be activated by antibodies, molecules of the adaptive system. The various cells of both systems work together through direct contact with each other, and through interactions with chemical mediators, the cytokines and chemokines (Section B2). These chemical mediators can be either cell-bound or released as localized **hormones**, acting over short distances. Cells of both systems have a large number of surface receptors: some are involved in adhesion of the cells to blood endothelial walls (e.g., leukocyte function antigen, LFA-1), some recognize chemicals released by cells (e.g., complement, cytokine, and chemokine receptors), and others trigger the function of the cell such as activation of the phagocytic process.

Adaptive immunity and clonal selection

All immunocompetent individuals have many distinct lymphocytes. Each of these cells is specific for a different foreign substance (**antigen**). Specificity results from the fact that each lymphocyte possesses cell-surface receptors all of which are specific for a particular antigen. When antigen is introduced into an individual, lymphocytes with appropriate receptors seek out and bind the antigen and are triggered to proliferate and differentiate into the effector cells of immunity (i.e., they give rise through division to large numbers of cells). All members of this **clone** of cells are specific for the antigen initially triggering the response and they, or their products, are capable of specifically reacting with the antigen or the cells that produce it and can mediate its elimination. In addition, there are a much larger number of cells specific for the immunizing antigen late in the immune response. These cells are able to respond faster to antigen challenge, giving rise to the "**memory**" involved in immunity. That is, individuals do not usually become infected by the same organism twice, as their immune system remembers the first encounter and protects against a second infection by the same organism. Of particular importance, all immunocompetent individuals have produced enough different specific lymphocytes to react with virtually every antigen with which an individual may potentially come in contact. How this diversity is developed is considered in Section D3.

Clonal selection as it applies to the B-cell system is shown in Figure 1 and is presented in more detail in Section E3. In particular, on encounter with antigen, B cells with receptors for that antigen bind and internalize it and receive help from T cells (Section F5). These B cells are triggered to proliferate, giving rise to clones of daughter cells. Some of these cells serve as memory cells, others differentiate and mature into **plasma cells**, which produce and secrete large quantities of specific antibody (Section C1).

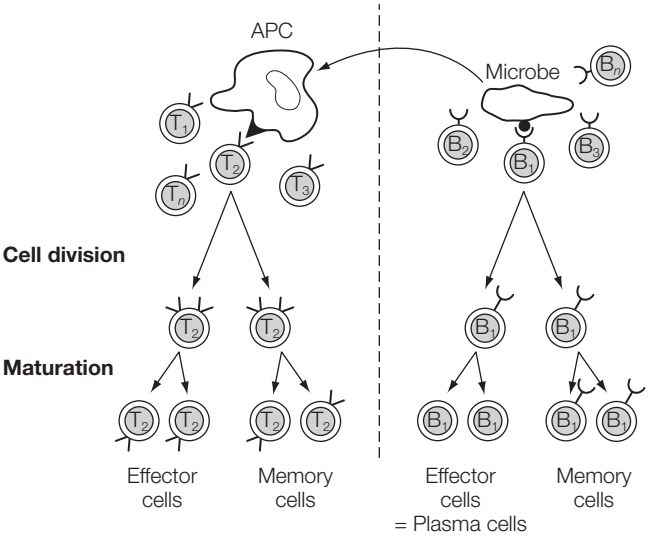

Figure 1. Clonal selection. From a large pool of B and T cells (T_n and B_n), antigen selects those which have receptors for it (e.g., T_2 and B_1) and stimulates their expansion and differentiation into memory and effector cells. Although B cells can recognize and bind native antigen, T cells only see antigen associated with MHC molecules on antigen-presenting cells (APC).

T and B cells and cell cooperation

The lymphocytes selected for clonal expansion are of two major types, B cells and T cells, each giving rise to different kinds of immunity. T lymphocytes mature under the influence of the thymus and, on stimulation by antigen, give rise to cellular immunity. B lymphocytes mature mainly under the influence of bone marrow and give rise to lymphoid populations which, on contact with antigen, proliferate and differentiate into **plasma cells**. These plasma cells make antibody (immunoglobulin) which is specific for the antigen and able to neutralize and/or eliminate it (humoral immunity).

The development of the immune response to an antigen also requires cell cooperation between cells of the immune system. T cells need to interact with both B cells and other antigen-presenting cells (APC) for the development of specific immune responses. Subpopulations of T cells help (Th cells) or suppress (Treg cells) antibody and cellular immune responses. Although immune responses to most antigens (especially proteins) require cell cooperation, some antigens (**T-independent**) are able to initiate an immune response in the absence of T lymphocytes.

A4 Antigens

Key Notes

Range of antigens

Antigens are defined as substances which induce an immune response. They include proteins, carbohydrates, lipids, and nucleic acids. Microbes have many different components which can be recognized by the innate and adaptive immune systems.

Antigen structures recognized by T and B lymphocytes

Antigens may contain a number of different antigenic determinants (epitopes) to which individual antibodies or T-cell responses are made. The smallest unit (antigenic determinant) to which an antibody can be made is about three to six amino acids or about five to six sugar residues. All large molecules have many determinants. Antibodies bind to conformational antigenic determinants (dependent on folding of the molecule) while T-cell receptors recognize linear amino acid sequences. Molecules which can stimulate an immune response ("immunogens") can be distinguished from those that react with antibodies but cannot initiate an immune response (haptens or individual antigenic determinants).

Related topics

(E1) The B-cell receptor complex, co-receptors, and signaling
(F2) T-cell recognition of antigen
(M2) Transplantation antigens

Range of antigens

The first stage of removing an invading organism is to recognize it as being foreign, that is, not "self" (Sections E and F). The immune system sees the invader as having a number of antigens. In the broad sense, an antigen is any substance which induces an immune response. Antigens recognized by cells of the innate immune system are called "pathogen-associated molecular patterns" (PAMPs) and initiate production of cytokines, chemokines, and antimicrobial peptides by these cells (Section B2). Recognition of antigens by lymphocytes results in proliferation and production of cytokines and/or antibodies. Antigens recognized by lymphocytes include proteins, carbohydrates, lipids, and nucleic acids. Responses can be made to virtually anything. Even self molecules or cells can act as antigens under appropriate conditions, although this is quite well regulated in normal healthy individuals (Section G).

Antigen structures recognized by T and B lymphocytes

It is usual that an antigen, a molecule which is capable of initiating an adaptive immune response, possesses several unique molecular structures, each of which can elicit an adaptive immune response. Thus, antibodies or cells recognizing an antigen are not directed against the whole molecule but against different parts of the molecule. These "antigenic determinants" or "epitopes" (Figure 1) are the smallest unit of an antigen to which an

antibody or cell can bind. For a protein, an antibody binds to a unit which is about three to six amino acids while for a carbohydrate it is about five to six sugar residues. Therefore, most large molecules possess many antigenic determinants per molecule, that is, they are "multideterminant." However, these determinants may be identical or different from each other on the same molecule. For example, a carbohydrate with repeating sugar units will have several identical determinants, while a large single chain protein will usually not have repeating 3–5 amino acid sequences, and will thus have many different antigenic determinants.

Although the linear sequence of the residues in a molecule has been equated with an antigenic determinant, the physical structures to which antibodies bind are primarily the result of the conformation of the molecule. As a result of folding, residues at different parts of the molecule may be close together and may be recognized by a B-cell receptor or an antibody as part of the same determinant (Figure 1). Thus, antibodies made against the native (natural) conformation of a molecule will not, in most instances, react with the denatured molecule even though the primary sequence has not changed. This is in contrast to the way in which T-cell receptors recognize antigenic determinants—in the form of linear amino acid sequences (Section F2), which have to be presented by major histocompatibility complex (MHC) molecules (Figure 2). The anchor amino acid residues of the linear peptide are important for attachment to the MHC molecule (Section F2).

In practical terms, microbes have a large number of different molecules and therefore potentially many different antigenic determinants, all of which could stimulate an immune response. However, all antigenic determinants are not equal—some may elicit strong and others weak responses. This is determined by the health, age, and genetics of the individual (Section G1).

Very small molecules, which can be viewed as single antigenic determinants, are incapable of eliciting an antibody response by themselves. These **haptens**, as they are called,

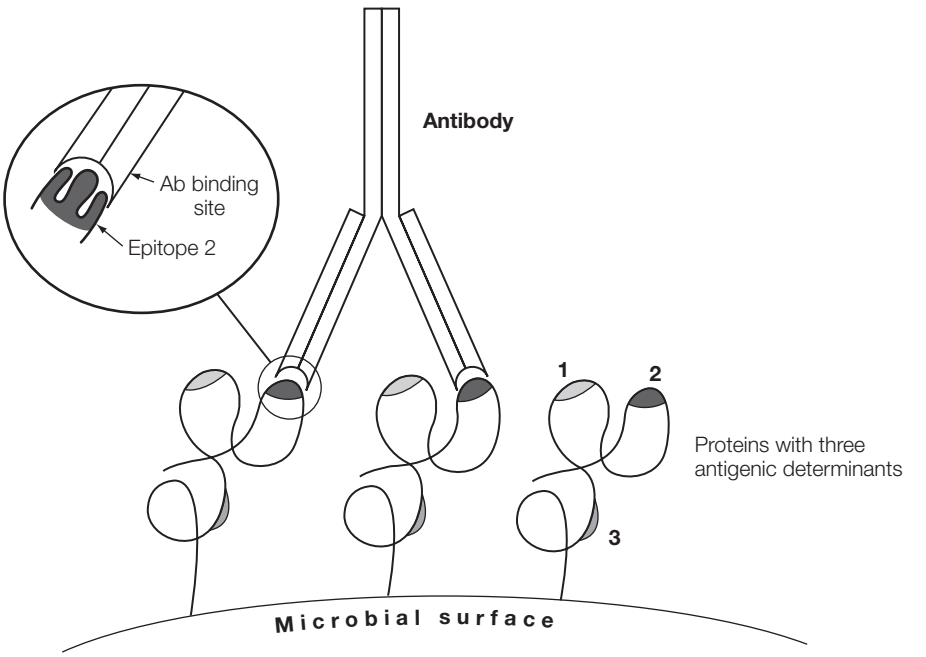

Figure 1. Antigenic determinants (epitopes) recognized by antibodies.

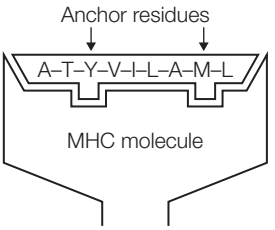

Figure 2. Linear sequence of peptides recognized by T cells.

can be attached covalently to larger molecules (**carriers**) and in this physical form can, with the help of T cells, induce the formation of antibodies. Therefore, one can distinguish between molecules which can stimulate an immune response (**immunogens**) and those which react with antibodies but cannot initiate an immune response (haptens or individual antigenic determinants).

A5 Hemopoiesis – development of blood cells

Key Notes

A common stem cell	The majority of the cell types involved in the immune system are produced from a common hemopoietic stem cell (HSC). HSCs are found in the fetal liver, fetal spleen, and in the neonate and adult bone marrow. They differentiate into functionally mature cells of all blood lineages.
Stromal cells	Direct contact with stromal cells (including epithelial cells, fibroblasts, and macrophages) is required for the differentiation of a particular lineage, as are adhesion molecules and cytokines.
Role of cytokines	Stromal cells produce many cytokines, including stem cell factor (SCF), monocyte colony-stimulating factor (M-CSF) and granulocyte colony-stimulating factor (G-CSF). Interaction of stem cells with stromal cells and M-CSF or G-CSF results in the development of monocytes and granulocytes, respectively.
Related topic	(B2) Molecules of the innate immune system

A common stem cell

The majority of cell types involved in the immune system are produced from a common hemopoietic stem cell (HSC) and develop through the process of differentiation into functionally mature blood cells of different lineages, for example monocytes, platelets, lymphocytes, and so forth (hemopoiesis: Figure 1). These stem cells are replicating self-renewing cells, which in early embryonic life are found in the yolk sac and then in the fetal liver, spleen, and bone marrow. After birth, the bone marrow contains the HSCs.

The lineage of cells differentiating from the HSC is determined by the microenvironment of the HSC and requires contact with stromal cells and interaction with particular cytokines. These interactions are responsible for switching on specific genes coding for molecules required for the function of the different cell types, for example those used for phagocytosis in macrophages and neutrophils, and the receptors on lymphocytes which determine specificity for antigens. This is, broadly speaking, the process of differentiation.

Stromal cells

Stromal cells, including epithelial cells and macrophages, are necessary for the differentiation of stem cells to cells of a particular lineage, for example lymphocytes. Direct

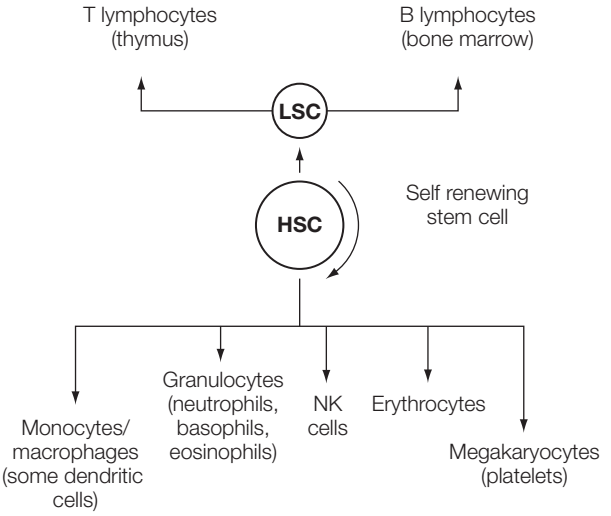

Figure 1. Origin of blood cells (hemopoiesis); LSC, lymphoid stem cell; HSC, hemopoietic stem cell; NK, natural killer.

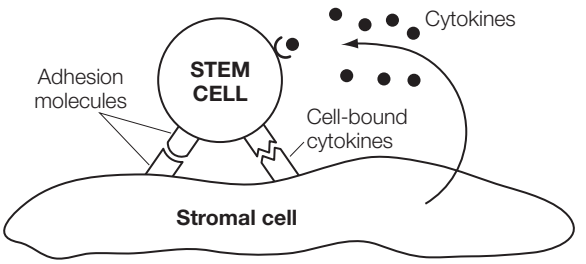

Figure 2. Role of stromal cells in hemopoiesis. Stromal-cell-bound cytokines (e.g., stem cell factor) and released cytokines (e.g., IL-7) determine the differentiation pathway of the stem cell attached through specific adhesion molecules (e.g., CD44) on the stem cell attached to hyaluronic acid molecules on the stromal cell.

contact of the stromal cell with the stem cell is required. Within the fetal liver, and in the thymus and bone marrow, different stromal cells (including macrophages, endothelial cells, epithelial cells, fibroblasts, and adipocytes) create discrete foci where different cell types develop. Thus, different foci will contain developing granulocytes, monocytes, or B cells. Cytokines are essential for this process, and it is thought that adhesion molecules also play an important role (Figure 2).

Role of cytokines

Different cytokines are important for renewal of HSC and their differentiation into the different functionally mature blood cell types. Although an oversimplification, the processes related to HSC regeneration depend largely on stem cell factor (SCF), interleukin-1 (IL-1), and IL-3. The development of granulocytes and monocytes require, among other cytokines, monocyte colony-stimulating factor (M-CSF) and granulocyte colony-stimulating factor (G-CSF), both of which are produced by stromal cells. Thus,

interaction of stem cells with stromal cells and with M-CSF or G-CSF results in the development of monocytes and granulocytes, respectively (Figure 3). Other cytokines are important for the early differentiation of T cells in the thymus and B cells in particular locations within the bone marrow.

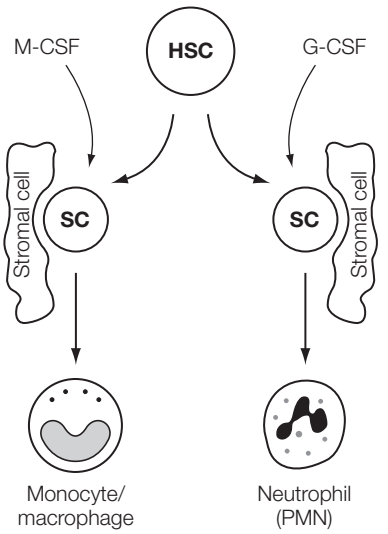

Figure 3. Different cytokines and stromal cells induce different pathways of differentiation. PMN, polymorphonuclear cell. SC, stem cell.

B1 Cells of the innate immune system

Key Notes

Phagocytes

Most white blood cells are mobile phagocytes (or eating cells), called neutrophils or polymorphonuclear cells (PMNs), that patrol the blood in search of invading microbes. Other primary phagocytic cells are part of the mononuclear phagocyte system, and include monocytes and macrophages. Monocytes are present in the blood and settle in the tissues as macrophages (MØ). These phagocytes are attracted to sites of infection (chemotaxis), bind to the microbe (adhere), and ingest (phagocytose) and kill the microbe. Molecules coating a microbe, such as complement or antibody, enhance contact and ingestion (opsonization) of the microbe.

Natural killer (NK) cells

NK cells are found throughout the tissues of the body but mainly in the circulation, and are important for protection against viruses and some tumors. Changes in the surface molecules of cells as the result of virus infection allow NK cells to bind to and kill infected cells by releasing perforins and inducing apoptosis. In addition, on binding to virus-infected cells, NK cells secrete interferon gamma (IFNγ), which protects adjacent cells from infection by viruses and helps to activate T-cell-mediated immunity.

Mast cells and basophils

Mast cells (in connective tissues) and basophils (in the circulation) are produced in the bone marrow and have similar morphology and functions. When activated, these cells degranulate, releasing pharmacological mediators resulting in vasodilation, increased vascular permeability, and leukocyte migration.

Dendritic cells (DCs)

DCs represent an important link between the innate and adaptive immune systems. Most interact with T cells through their expression of MHC class II molecules while others (follicular dendritic cells) interact with B cells in the B-cell follicles of the lymphoid tissues. Those that interact with T cells are either myeloid DCs or plasmacytoid DCs, so called because they look like plasmacytes. Immature myeloid DCs pick up antigen and transport it to the lymphoid tissues. The main property of plasmacytoid DCs is their ability to produce large amounts of type I interferons following activation by viruses. Both types of DCs are involved in inducing and regulating immune responses.

NKT cells	Although these cells have many of the properties of NK cells they also have some T-cell characteristics, making it difficult to classify them as innate immune cells. Expressing CD3 and using a limited T-cell receptor gene repertoire, they respond to lipids and glycolipids but not peptides, which are recognized by most T cells. They recognize antigens displayed on CD1d (not conventional MHC molecules) expressed by antigen-presenting cells. Like NK cells, they can be cytotoxic, but produce a wider spectrum of cytokines than NK cells that function to regulate immune responses.
Other cells playing a role in innate immunity	A variety of other cells, including epithelial cells, eosinophils, platelets, and erythrocytes play a role in immune defense. Epithelial cells produce antimicrobial peptides. Eosinophils are granular leukocytes that attack and kill parasites by releasing the toxin major basic protein. Platelets, on activation, release mediators that activate complement leading to attraction of leukocytes. Erythrocytes bind and remove small immune complexes.
Related topics	(D2) Antibody classes (D8) Antibody functions (F2) T-cell recognition of antigen (H1) The microbial cosmos (K2) IgE-mediated (type I) hypersensitivity: allergy

Phagocytes

Phagocytes are specialized "eating" cells (*phagein*: Greek, "to eat"), of which there are two main types, neutrophils and macrophages. **Neutrophils**, often called polymorphonuclear cells (PMNs) because of the multilobed nature of their nuclei (Figure 1), are mobile phagocytes that comprise the majority of blood leukocytes (about 8×10^6 per ml of blood). They have a very short half-life (days) and die in the bloodstream by apoptosis

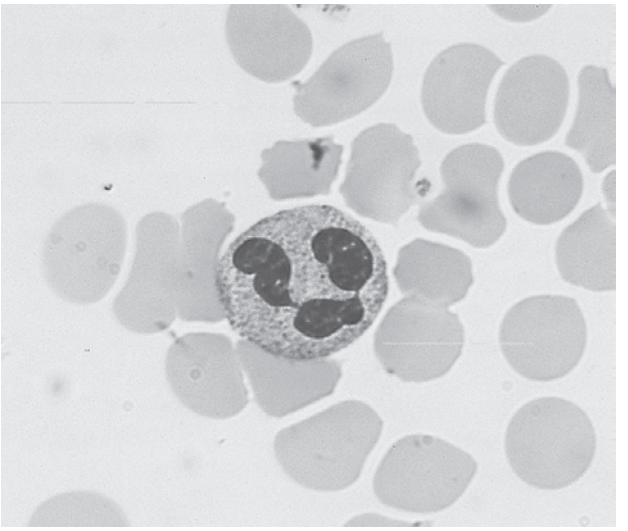

Figure 1. A polymorphonuclear cell (neutrophil) in the blood. From Male D, Brostoff J, Roth D & Roitt I (2006) Immunology, 7th ed. With permission from Elsevier.

(programmed cell death). They have granules that contain peroxidase, alkaline and acid phosphatases, and defensins (Section B2), which are involved in microbial killing. These granulocytes stain with neutral dyes and have a different function from granulocytes that stain with eosin (eosinophils) or basic dyes (basophils). PMNs have receptors for chemotactic factors released from microbes, for example muramyl dipeptide (MDP), and for complement components activated by microbes (Table 1). Their main function is to patrol the body via the bloodstream in search of invading microbes. As such they are pivotal cells in acute inflammation (Section B4). Like the majority of cells involved in the immune system, these phagocytes are produced in the bone marrow (Section A5).

The **mononuclear phagocyte system** (previously called the reticuloendothelial system) is a widely distributed tissue-bound phagocytic system whose major function is to dispose

Table 1. Surface receptors on polymorphonuclear cells (PMNs)

Surface molecules	Function
Pattern recognition receptors	
TLRs*, NLRs, and MR	Recognize PAMPs; trigger cytokine production and cell activation
Complement receptors	
CR1 (CD35)	Binds to C3b, iC3b, C4b, and mannose binding ligand (opsonization)
CR3 (CDIIb/CD18)	Binds to C3b, iC3b; permits removal (opsonization) of complement coated antigens and microbes
Fc receptors for IgG	
CD16 (FcγRIII), CD32 (FcγRII)	Binds to IgG–antigen complexes (opsonization)
CD64 (FcγRI)	Expressed on activated PMNs (opsonization)
Chemokine receptors	
CXCR1 and CXCR2	Binds IL-8 produced by macrophages and epithelial cells
Chemoattractant receptors	
C5aR	Binds to C5a for attraction towards microbes after C activation
Leukotriene B4 receptors	LTB4 produced from leukocytes and necrotic cells
Receptors for FMLP	FMLP produced by breakdown of some bacterial proteins
Receptor for MDP (NOD2)	MDP is a peptidoglycan constituent of both Gram-positive and Gram-negative bacteria (see above and Sections B2 and B3)
Adhesion receptors	
LFA-1	Binds to ICAM-1 on endothelium for extravasation
VLA-4	Binds to VCAM-1 on endothelium for extravasation

TLR ,Toll-like receptor; NLR, nucleotide-binding oligomerization domain-like receptor; MR, mannose receptor; PAMPs, pattern associated molecular pattern; FMLP, formyl-methionyl-leucyl-phenylalanine; MDP, muramyl dipeptide; LFA-1, leukocyte function antigen-1; ICAM-1, intercellular adhesion molecule-1; VLA-4, very late activation antigen-4; VCAM-1, vascular cell adhesion molecule-1. * Some TLRs and all NLRs are intracellular receptors. NOD2 is one of the NLRs.

of microbes and dead body cells through the process of phagocytosis. Monocytes (Figure 2) are blood-borne precursors of the major tissue phagocytes, macrophages. Different organs/tissues each have their versions of monocyte-derived phagocytic cells (Table 2).

Phagocytosis is a multistep process (Table 3) and the major mechanism by which microbes are removed from the body. It is especially important for defense against extracellular microbes (Section H2).

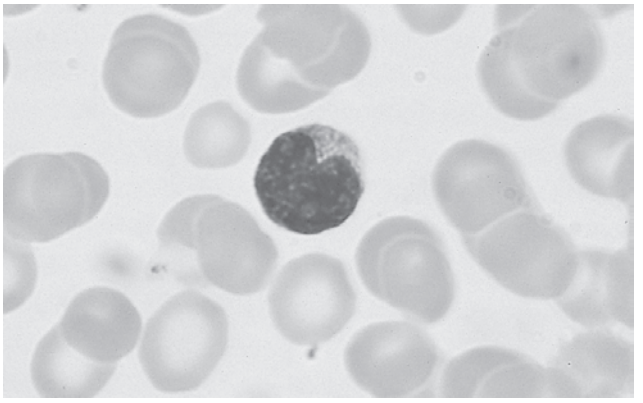

Figure 2. A monocyte in the blood. From Roitt I, Brostoff J & Male D (1998) Immunology, 5th ed. With permission from Elsevier.

Table 2. Cells of the mononuclear phagocyte system

Cells	Location
Monocytes	Bloodstream
Kupffer cells	Liver
Mesangial cells	Kidney
Alveolar macrophages	Lungs
Microglial cells	Brain
Sinus macrophages	Spleen, lymph nodes
Serosal macrophages	Peritoneal cavity

Table 3. Stages in phagocytosis

Stage	Mechanism
1 Movement of phagocyte towards the microbe	Chemotactic signals, e.g., MDP, complement (C5a)
2 Attachment of microbe to the phagocyte surface	Binding to mannose, complement and/or Fc receptors
3 Endocytosis of microbe leads to the formation of a phagosome	Invagination of surface membrane
4 Fusion of phagosome with lysosome	Microtubules involved
5 Killing of microbe	Oxygen-dependent killing, e.g., O_2 radicals, nitric oxide; oxygen-independent, e.g., myeloperoxidase

Opsonization is the process of making a microbe easier to phagocytose. A number of molecules called "opsonins" (*opsonein*: Greek, "to buy provisions") do this by coating the microbe. They aid attachment of the microbe to the phagocyte and also trigger activation of phagocytosis. Opsonins include the complement component C3b and antibody itself, the latter acting as a bridge between the innate and adaptive immune systems (Sections B2 and D8). Mononuclear phagocytes use their surface receptors (Table 4), which bind to C3b or to the Fc region of IgG antibody (Fc receptors, FcγR), to attach to C3b or IgG coating the microbes, respectively.

Killing by mononuclear phagocytes is generally very efficient, as there are many cytotoxic mechanisms available to these cells. In particular, these cells contain many different

Table 4. Surface receptors on monocytes/macrophages

Surface molecules	Function
Pattern recognition receptors	
TLRs*, NLRs, MRs, and others	Mediate cytokine production and induce adaptive immune responses. Some mediate phagocytosis
Fc receptors for IgG	
CD16 (FcγRIII), CD32 (FcγRII), CD64 (FcγR1)	Binds to IgG–antigen complexes and IgG-coated target cells, mediating phagocytosis and cytokine production
Fc receptor for IgA	
CD89 (FcαR)	Binds to IgA–antigen complexes, mediating phagocytosis and cytokine production
Complement receptors	
CD35 (CR1)	Involved in enhancing phagocytosis of IgM/IgG-coated microbes on which complement has been activated (opsonization)
CR3 (CDIIb/CD18)	Binds to C3b, iC3b; permits removal of complement-coated antigens and microbes (opsonization)
Adhesion receptors	
CD18/11a,b,c (LFA-1, CR3, CR4)	Adhesion molecules facilitating interactions with other cells, including binding to endothelial cells for extravasion (monocytes)
VLA-4	Binds to VCAM-1 on endothelial cells for extravasion (monocytes)
Antigen presentation molecules (HLA)	
MHC class I (HLA A,B,C)	Presentation of peptides to Tc cells
MHC class II (HLA D)	Presentation of peptides to Th cells
(MHC-like) CD-1	Presentation of lipids to NKT cells**

TLR, Toll-like receptor; NLR, nucleotide-binding oligomerization domain-like receptor; MR, mannose receptor; PAMP, pattern associated molecular pattern; FMLP, formyl-methionyl-leucyl-phenylalanine; MDP, muramyl dipeptide; LFA-1, leukocyte function antigen-1; VLA-4, very late activation antigen-4; VCAM-4, vascular cell adhesion molecule-4.
*Some TLRs and all NLRs are intracellular.
**To be dealt with in Section C.

enzymes, cationic proteins and antimicrobial peptides (defensins: Section B2) that in concert can mediate killing and digestion of the microbe. In addition, on activation, these mononuclear phagocytes can kill intracellular pathogens via oxygen-dependent mechanisms through oxygen metabolites, including superoxide and nitric oxide.

Natural killer (NK) cells

Natural killer (NK) cells differ from classical lymphocytes in that they are larger, contain more cytoplasm, and have (electron) dense granules (Figure 3). Produced in the bone marrow, they are found throughout the tissues of the body, but mainly in the circulation where they comprise 5–15% of the total lymphocyte fraction (Section C1). Their cell surface receptors (Table 5) include killer activation receptors (KARs) and killer inhibitory receptors (KIRs). These interact with molecules on body cells that activate or inhibit NK cell activity, respectively. FcγRIII on these cells mediates antibody-dependent cellular cytotoxicity (ADCC) of antibody-coated microbes/tumor cells. There are also some cell adhesion molecules involved in activation and traffic of NK cells. Toll-like receptors (TLRs: Section B3) on NK cells contribute to activation of cytotoxicity and cytokine production.

The main function of NK cells is to kill virus-infected self cells, as well as some tumor cells. When NK cells bind to uninfected self cells, their KIRs provide a negative signal to the NK cell, preventing it from killing the self cell. This is because KIRs recognize MHC class I (Section F2) leader peptides presented in an MHC-like molecule, human leukocyte antigen-E (HLA-E). However, infection of cells by some viruses reduces the expression of MHC molecules, and therefore decreases the loading of class I peptides in HLA-E, thus allowing the activation through KARs to induce NK-cell killing of the infected cell. This is an important mechanism, allowing NK cells to recognize normal self cells and ignore them, while killing infected or malignant self cells.

The mechanisms by which NK cells mediate killing are identical to those used by cytotoxic T cells (Section F5) and involve release of granule contents (perforins and granzymes) onto the surface of the infected cell. Perforin has a structure similar to that of C9, a component of complement which can create pores in the cell membrane (Sections B2 and D8), allowing the passage of the granzymes (proteolytic enzymes) into the cell to induce apoptosis. NK cells, like cytotoxic T cells, are also able to induce target cell

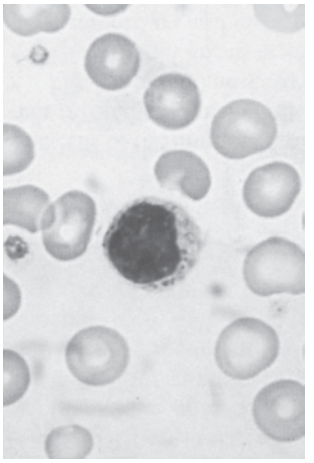

Figure 3. An NK cell in the blood. From Male D, Brostoff J, Roth D & Roitt I (2006) Immunology, 7th ed. With permission from Elsevier.

Table 5. Surface receptors on natural killer cells

Molecules	Function
Activation/inhibitory receptors	
KIRs	Contain ITIMs and bind to MHC class-I-like molecules associated with self peptide and prevent NK cells from killing
KARs	Bind to self antigens (e.g., carbohydrate on self cells) and are associated with other molecules that contain ITAMs. On activation by KAR binding (in the absence of simultaneous engagement of KIRs) they initiate release of cytotoxic molecules from the NK cells
Fc receptors	
CD16 (FcγRIII)	Binds to IgG-coated target cells and mediates ADCC
Adhesion/accessory molecules	
CD2	Binds to LFA-3
CD56 (NCAM)	Binds to FGFR-1 that is bound to and secreted by fibroblasts
LFA-1	Binds to ICAM-1

KIR, killer inhibitory receptor; KAR, killer activation receptor; ADCC, antibody-dependent cellular cytotoxicity; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITAM, immunoreceptor tyrosine-based activation motif; NCAM, neural cell adhesion molecule; LFA-3, leukocyte function antigen-3; FGFR-1, fibroblast growth factor receptor-1; ICAM-1, intercellular adhesion molecule-1.

apoptosis through binding of their surface FasL molecules to Fas molecules on the surface of the virus-infected cell (Section F5).

IL-2 activates NK cells to kill, and these lymphokine-activated killer (LAK) cells have been used in clinical trials to treat tumors (Section N5). When NK cells are "activated" by recognizing a virus-infected cell they secrete IFNγ. This helps to protect surrounding cells from virus infection, although IFNα and IFNβ are probably more important in this role (Section B2). In addition, IFNγ can also enhance the development of specific T-cell responses directed to virus-infected cells (Sections F4 and F5).

Mast cells and basophils

Mast cells (Figure 4) are found throughout the body in connective tissues close to blood vessels and particularly in the subepithelial areas of the respiratory, genitourinary, and gastrointestinal tracts. Basophils are granulocytes which stain with basic dyes and are present in very low numbers in the circulation (<0.2% of the granular leukocytes). Basophils and mast cells are very similar in morphology. Both have large characteristic electron-dense granules in their cytoplasm which are very important for their function. Like all the granulocytes, basophils and mast cells are produced from stem cells in the bone marrow.

Mast cells/basophils can be stimulated to release their granules as a result of:

- Their binding to the anaphylatoxins C3a and C5a
- Binding of allergens to antiallergen IgE bound to their cell surface Fc receptor (FcεR) and the resulting crosslinking of FcεR (Section K2)

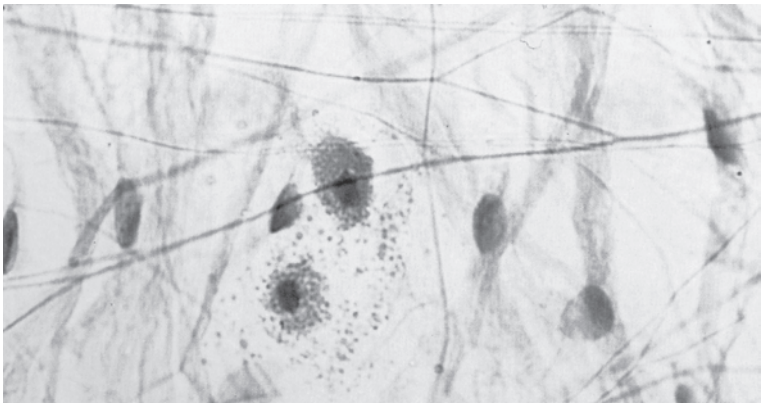

Figure 4. Mast cells. Note the large granules in the cytoplasm which contain pharmacological mediators. From Leboffe MJ & Pierce BE (1996) A Photographic Atlas for the Microbiology Laboratory. With permission from Morton Publishing.

- Binding to lectins (molecules that bind carbohydrates)
- Some drugs (e.g., opioids, succinylcholine, vancomycin) as well as radiocontrast agents

Stimulation results in the fusion of the intracellular granules with the surface membrane and the release of their contents to the exterior by the process of exocytosis. This release is almost instantaneous and is essential in the development of the acute inflammatory response (Section B4). Granule contents include a variety of preformed pharmacological mediators. Other pharmacological mediators are produced *de novo* when the cells are stimulated (Table 6). Production *de novo* of pro-inflammatory cytokines such as TNFα and IL-8 can be induced through binding of microbial products to TLRs expressed on mast cells (Section B3). When large numbers of mast cells/basophils are stimulated to degranulate, severe anaphylactic responses can occur, which in their mildest form give rise to the allergic symptoms seen in type I hypersensitivity (Section K2).

Dendritic cells (DCs)

These are cells that link the innate and adaptive immune systems. Dendritic cells (DCs) are so called because of their many surface membrane folds that are similar in appearance to dendrites of the nervous system (Figure 5). These folds allow maximum interaction with other cells of the immune system. Dendritic cells can be divided into two major groups: (i) those expressing high levels of MHC class II for antigen presentation to T cells;

Table 6. Main mediators released and their effects

	Mediators	Effect
Preformed	Histamine	Vasodilation, vascular permeability
De novo synthesized	Cytokines, e.g.	
	TNFα, IL-8, IL-5	Attract neutrophils and eosinophils
	PAF	Attracts basophils

TNFα, tumor necrosis factor α; IL, interleukin; PAF, platelet-activating factor.

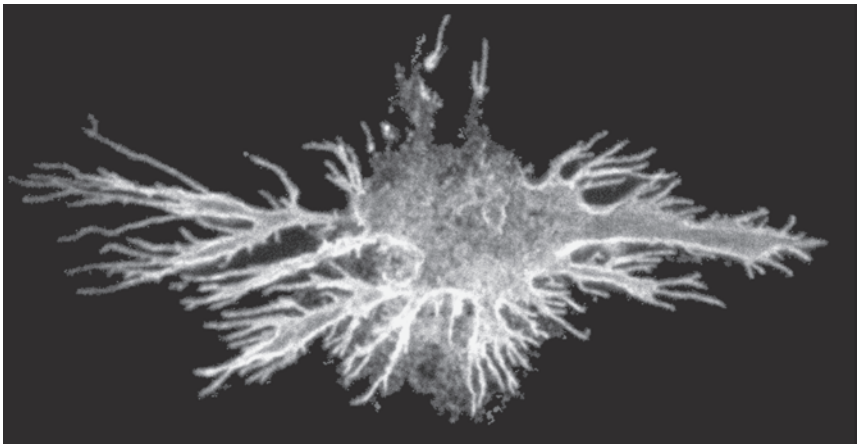

Figure 5. Dendritic cell. Note the many membrane processes that allow interactions with lymphocytes. Surface stained with a fluorescent antibody to CD44 (shown white). CD44 is an adhesion molecule that allows the dendritic cell to attach to connective tissue and other cells. (Figure courtesy of M. Binks.)

(ii) those in the follicles of lymphoid tissues (follicular dendritic cells, FDC) that do not express MHC class II but have other markers able to interact with B cells (Section C2).

The DCs that present antigen to T cells ((i) above) can be further divided into myeloid-derived DCs or plasmacytoid DCs, so called because they look like plasmacytes. The main characteristics of these DC populations are shown in Table 7.

DCs represent a primary interface between the innate and adaptive immune systems in that they recognize microbial antigens through pattern recognition receptors (PRRs), and through cytokine production and antigen processing and presentation they are able to initiate adaptive immune responses by presenting peptide antigens to T-helper ($CD4^+$) cells.

Since the T-cell antigen receptor can only recognize "pieces" of proteins in association with MHC molecules, proteins first need to be "processed" (cut up into short peptides). These peptides are then attached to MHC molecules (Section F2) for display on the

Table 7. Dendritic cells

Classification	Characteristics	Function
Myeloid*	Localized in blood and tissues. Relatively short lived and replenished by bone marrow precursors	Phagocytic when immature; migrate to lymphoid organs and tissues; main antigen presenting cells to prime $CD4^+$ T cells; regulate immune responses
Plasmacytoid	Present in bone marrow and peripheral organs: usually long lived	Produce large amounts of type I interferons following exposure to viruses; can present antigen to $CD4^+$ T cells and regulate immune responses

*Langerhans cells (LH) are classified as myeloid-cell-derived DCs, but are found in the epidermis of the skin. Interdigitating cells of the T-cell areas of the secondary lymphoid tissues are also of this type (Section C2).

surface of myeloid and plasmacytoid DCs. Although macrophages can process and present antigen to T cells, the conventional DCs are much more efficient in carrying out this function. Some DCs can also act to induce T-cell tolerance to antigens (especially self), a very important mechanism leading to peripheral tolerance to self antigens (Section G3).

NKT cells

These cells are difficult to classify as innate immune cells because although they have many of the properties of NK cells they also have some T-cell characteristics. They express CD3, but unlike conventional T cells that recognize peptides, NKT cells recognize and respond to lipid and glycolipid antigens. These are presented to them, not in a conventional MHC context (i.e., MHC class I and II molecules) but rather a nonpolymorphic MHC-like molecule, CD1d. They also possess a relatively invariant αβ T-cell receptor using biased rearranged T-cell receptor genes (Section F3). Like NK cells, they can be cytotoxic, but they produce a wider spectrum of cytokines than NK cells, which function to regulate immune responses.

Other cells playing a role in innate immunity

Epithelial cells lining the digestive, respiratory, and genitourinary tracts produce and secrete a variety of antimicrobial peptides (Section B2).

Eosinophils are granular leukocytes which stain with eosin. They are present at low levels in the circulation (2–5% of blood leukocytes), have some phagocytic activity, but are primarily responsible for extracellular killing of large parasites (e.g., schistosome worms) that cannot be phagocytosed (Section H2). They usually bind to an antibody-coated parasite through surface Fc receptors and release the contents of their granules (degranulate) onto the parasite surface. The granules contain peroxides and a toxin, major basic protein, which kill the parasite. Histaminase is also present in the granules. This anti-inflammatory substance dampens the effects of histamine released by mast cells earlier in the response.

Platelets, as well as having a major role in blood clotting, contain important mediators that are released when they are activated at the site of a damaged blood vessel. Parasites coated with IgG and/or IgE antibodies are also thought to activate platelets through surface Fc receptors for these antibody classes. Released mediators activate complement, which in turn attracts leukocytes to the site of tissue damage caused by trauma or infection by a parasite (Section B4).

Erythrocytes have surface complement receptors that bind to complement attached to small circulating immune complexes. They carry these complexes to the liver, where they are released to Kupffer cells which phagocytose them. Thus, erythrocytes play an important immunological role in clearing immune complexes from the circulation in persistent infections and in some autoimmune diseases.

B2 Molecules of the innate immune system

Key Notes

Innate molecular immune defense

A variety of molecules mediate protection against microbes during the period before adaptive immunity develops. These include antimicrobial peptides, complement, acute phase proteins, and cytokines. Many of these components are also required for the development of a functional adaptive immune system and highlight the interdependence of the two systems.

Antimicrobial peptides (AMPs)

AMPs are small peptides important to innate immune defense against a wide spectrum of microbes (Section C3). They are produced by epithelial cells that line the respiratory, gastrointestinal, and genitourinary tracts of the body, and by phagocytic cells once the microbes have breached the epithelial cell barrier.

The complement system

The complement system consists of over 20 interdependent proteins, which on sequential activation mediate protection against infection by some microbes. Synthesized by hepatocytes and monocytes, these proteins can be activated directly by microbes through the **alternative pathway** and thus have a pivotal role in innate immunity. This system can also be activated through the **classical pathway** by antibodies (adaptive immunity) and by lectin-like molecules bound to a microbe, the **lectin pathway**. On activation, the complement system can (i) initiate (acute) inflammation; (ii) attract neutrophils to the site of microbial attack (chemotaxis); (iii) enhance attachment of the microbe to the phagocyte (opsonization); (iv) kill the microbe.

Acute phase proteins

Acute phase proteins are a heterogeneous group of plasma proteins important in innate defense against microbes (mostly bacteria) and in limiting tissue damage caused by infection, trauma, malignancy, and other diseases. They include C-reactive protein (CRP), serum amyloid protein A (SAA), and mannose-binding protein (MBP). Acute phase proteins are mainly produced in the liver, usually as the result of a microbial stimulus, or in response to the cytokines IL-1, IL-6, TNFα, and IFNγ that are released by activated macrophages and NK cells. These proteins maximize activation of the complement system and opsonization of invading microbes.

Overview of cytokines

Cytokines are small molecules that signal between cells, inducing growth, chemotaxis, activation, enhanced cytotoxicity, and/or regulation of immunity. Many of them are classified as interleukins as they are primarily produced by, and communicate with, leukocytes. Other groups include the chemokines that direct cell migration and the interferons that protect against viral infection, activate cells, and modulate immunity.

Interleukins

The interleukins, originally categorized by their ability to communicate between leukocytes, are growth and differentiation factors for immune cells. Other interleukins have pro-inflammatory activities that together with other cytokines are critical to immune defense and inflammation.

Chemokines

Chemokines are small cytokines produced by many cell types in response to infection or physical damage. They activate and direct effector cells expressing appropriate chemokine receptors to migrate to sites of tissue damage and regulate leukocyte migration into tissues. CC chemokines are chemotactic for monocytes, while CXC chemokines are chemotactic for PMNs.

Interferons

Interferons (IFNs) are produced in response to viral infection and inhibit protein synthesis. Type I IFNs (IFNα and IFNβ) are produced by many different cells. Type II interferon (IFNγ), mainly produced by Th1 cells and NK cells, induces Th1 responses, increases antigen presentation, and activates phagocytic and NK cells for enhanced killing.

Other cytokines

Other cytokines include colony-stimulating factors (CSFs) that drive development, differentiation, and expansion of cells of the myeloid series. GM-CSF induces commitment of progenitor cells to the monocyte/granulocyte lineage, and G-CSF and M-CSF commitment to the granulocyte and monocyte lineages, respectively. Transforming growth factor β (TGFβ) inhibits activation of macrophages and growth of B and T cells. Tumor necrosis factor β (TNFβ) is cytotoxic.

Related topics

(A2) External defenses
(A5) Hemopoiesis – development of blood cells
(B1) Cells of the innate immune system
(B4) Innate immunity and inflammation
(C1) Lymphocytes
(E2) B-cell activation
(F2) T-cell recognition of antigen
(F4) T-cell activation
(F5) Clonal expansion and development of memory and effector function
(G5) Regulation by T cells and antibody
(G6) Neuroendocrine regulation of immune responses
(H2) Immunity to different organisms